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The Berkeley Contact Lens Extended Wear Study: Part I

Study Design and Conduct

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Objective: The primary aim of the Berkeley Contact Lens Extended Wear Study (CLEWS) was to test the hypotheses that extended wear of rigid gas-permeable (RGP) contact lenses with greater oxygen permeability (Dk) reduces the incidence of contact lens–associated keratopathy (CLAK) and increases the survival rate in RGP extended wear (EW). In this article we describe the clinical trial design in detail, present the results of subject recruitment and retention, and provide the baseline demographic and ocular characteristics of the CLEWS subjects, whose data will be analyzed to address the study aims in a companion article.

Design: A randomized, concurrently controlled clinical trial.

Intervention: Subjects were fitted with day wear (DW) high-Dk RGP lenses and then adapted to EW. Subjects who adapted to EW were then randomly assigned to either high- or medium-Dk RGP lenses for 12 months of 6-nights/week EW.

Main Outcome Measures: Slit-lamp assessment and grading of 17 possible keratopathies, measurement of refractive error and corneal curvature, and symptoms. Follow-up data were collected every 3 months.

Results: From 545 subjects entering the DW adaptation phase, 201 adapted to EW and were randomly assigned to medium- or high-Dk lenses for 12 months of EW. The baseline characteristics of the two study groups were similar and did not differ from the 344 DW subjects who failed to adapt to EW. The distributions of oxygen transmissibility for the two study groups were disjoint, indicating that each group received distinctly different levels of hypoxia.

Conclusions: We show that CLEWS was appropriately designed to address the study hypotheses, was conducted with regard for the safety of the subjects, and adhered to rigorous protocols designed to control for bias and ensure the integrity of study data. We establish the internal validity of between-group statistical comparisons and characterize our study population to permit informed evaluation of the applicability of our results to the contact lens–wearing population in general. *Ophthalmology 2001;108:1381–1388 © 2001 by the American Academy of Ophthalmology.*

Contact lens (CL) extended wear has been associated with the development of various corneal complications, some of which can cause permanent visual impairment.[1–5] Concerns about the risks associated with CL wear have resulted in considerable research aimed at ameliorating CL-associated keratopathy. Several studies have shown an association between wearing lenses known to cause corneal hypoxia and the occurrence of adverse corneal events such as increased epithelial cell loss,[4] inflammation,[5] microbial keratitis,[1,2] acute red eye,[4] and endothelial polymegethism.[6] Under controlled laboratory testing conditions, decreased lens oxygen transmissibility (Dk/t) has been associated with increased corneal swelling,[7,8] increased binding of *Pseudomonas aeruginosa* to epithelial cells (Cavanagh HD, Ren H, Ladage PM, et al. Invest Ophthalmol Vis Sci 40:S906, 1999), decreased desquamation rates of epithelial cells,[9] impaired corneal volume regulation,[10] and lowered corneal pH.[11]

On the basis of these findings, many clinicians and researchers have assumed that the incidence and severity of CL-related adverse events depend in part on the hypoxic dosage (i.e., oxygen tension at the tear-lens interface) that the cornea receives during overnight lens wear. Although these studies provide evidence for a hypoxic mechanism, further research is required to clearly demonstrate a link between hypoxic dosage and either the incidence of complications or the ability to maintain successful CL extended wear. Determining whether there is a dose-response rela-

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tionship between the risk of keratopathy and corneal hypoxia, or whether, for example, the risk is uniformly increased given some threshold hypoxic level, has implications for understanding the mechanisms associated with CL-associated keratopathy, as well as for the design and clinical use of CLs.

This uncertainty about the exact relationship between hypoxia and adverse ocular response in overnight CL wear prompted our corneal research group to undertake the Berkeley Contact Lens Extended Wear Study (CLEWS). CLEWS was a randomized, concurrently controlled clinical trial involving comprehensive quarterly follow-up of more than 200 subjects randomly assigned to wear either medium- or high-oxygen permeable (Dk) rigid gas-permeable (RGP) lenses for 12 months of extended wear (EW). The primary aims of CLEWS were to determine whether wearing high oxygen-permeable RGP lenses for extended wear (1) lowers the incidence of CL-associated keratopathy, and (2) reduces the rate at which subjects discontinue overnight wear because of lens-related complications. Secondary aims of the study were to assess the effects of hypoxic dosage on various laboratory measures of corneal structure and function, to identify possible predictors of RGP EW–associated keratopathy, and to develop a semiautomated data management and quality assurance system for clinical research. CLEWS lasted for approximately 5 years, from the beginning of recruitment in April 1994 to the end of data collection in July 1999.

The purposes of this first article are to (1) present the main features of the CLEWS clinical trial design; (2) describe the recruitment, measurement, and bias control strategies; and (3) present the results of subject recruitment, retention, and baseline assessments, which are necessary to define the CLEWS study population and permit interpretation of subsequent statistical results. We analyze in a companion article (Polse KA, Graham AD, Fusaro RE, et al, The Berkeley Contact Lens Extended Wear Study. Part II: Clinical Results) the clinical outcomes to address the primary study aims. Secondary aims of CLEWS will be addressed in several other separate articles.

Material and Methods

CLEWS was designed with three main stages: screening and baseline evaluation (stage 1), adaptation to CL wear (stage 2), and randomized lens wear and follow-up (stage 3). We first describe these three stages in detail, outline the bias control measures used in CLEWS, and describe the changes in protocol made during the course of the trial. We then describe the study lenses, personnel, and procedures, including data management and quality assurance and external interim review of CLEWS conduct by a Data and Safety Monitoring Board (DSMB).

The CLEWS Clinical Trial Design

Stage 1. Screening and Baseline Evaluation

Prospective subjects were recruited from the San Francisco Bay Area and the general University of California at Berkeley (UCB) community through newspaper advertisements, fliers, UCB School of Optometry clinic referrals, and direct referrals.

Table 1. Contact Lens Extended Wear Study Eligibility Criteria at Date of Initial Orientation. (Subjects Who Met These Screening Criteria Were Then Scheduled for a Clinical Examination and Diagnostic Lens Fitting to Determine Final Eligibility to Participate in Contact Lens Extended Wear Study and to Enter the Lens Wear Adaptation Phase [Stage 2]).

1. Age: 18 to 39
2. Ocular health: normal
3. Refractive error: +7.00 to −9.00 diopter spherical, and 0.00 to −1.75 diopter cylindric
4. Residence: San Francisco Bay Area for at least the next 1.5 yrs
5. Ocular or medical history: no conditions or injuries that might adversely affect ocular health or otherwise limit ability to wear contact lenses
   - Corneal surgery, corneal trauma
   - Medications, including antidepressants, steroids
   - Allergies with pronounced ocular effects (e.g., tearing, itching)
6. History of overnight polymethyl methacrylate contact lens wear: none
7. History of or current daily contact lens wear: minimal or none
   - < 6 months total wearing time, or
   - Currently wearing, or discontinued ≤ 6 mos ago
     - Worn ≤ 12 mos, < 30 hs/wk average
     - Worn > 12 mos, < 15 hs/wk average
   - Discontinued wear > 6 mos ago
     - Worn ≤ 24 mos, < 30 hs/wk average
     - Worn > 24 mos, < 15 hs/wk average

All subjects attended an orientation meeting at which information about age, gender, ethnicity, occupation, medical history, and previous CL experience was collected, the current spectacle prescription measured, and keratometry readings obtained. Table 1 lists the eligibility criteria used in stage 1 to accept or reject prospective subjects.

Because some types of CL wear have been shown to affect corneal structure and function,[10,12] we initially attempted to enroll only subjects with no previous CL experience; however, unanticipated difficulties in enrolling eligible subjects for full participation in CLEWS prompted us to accept subjects with some minimal CL experience (as defined in Table 1). No prior polymethylmethacrylate or overnight CL wear was permitted. Day wear of RGP or soft lenses was permitted if the subject had worn CLs for less than 6 months total wearing time. For subjects with longer total time in CL wear, a set of rules was applied that accounted for how recently and how many hours per week, on average, lenses were worn. We believe these criteria reflected minimal CL experience that was unlikely to have had a negative impact on the cornea before participation in CLEWS.

Subjects who met the initial screening criteria were then given a detailed explanation of the study procedures, followed by a comprehensive eye and CL fitting examination. Those subjects meeting all study eligibility criteria then proceeded to stage 2. Informed consent, as approved by the UCB Committee for Protection of Human Subjects, was obtained from each participant.

Stage 2. Adaptation to Contact Lens Wear

In stage 2, subjects adapted first to day wear of high-Dk RGP lenses and, if successful, then proceeded to EW adaptation, following standard clinical procedures.[13] All subjects wore the high-Dk lenses throughout stage 2 to avoid any bias that could arise if subjects were to begin adaptation with their assigned study lenses (i.e., medium- or high-Dk) and then experienced differing group success rates in adaptation. Beginning with 4 hours on the first day, wearing time was increased by 2 hours/day until 8

hours/day was reached. At approximately 1-week intervals thereafter, subjects reported for follow-up examinations that included history, visual acuity, lens assessment, keratometry, and slit-lamp assessment. Lens changes were made when indicated to help the patient achieve full-time day wear (14–16 hours/day). Additional information on the day wear adaptation phase of this trial has been reported elsewhere.[14]

On successful adaptation to full-time day wear, the subjects attempted overnight wear and reported in the morning after the first and fourth nights for clinical evaluations. If the subjects had no difficulty with overnight wear (e.g., no discomfort, no red eye) and the clinical assessments revealed no complications, a 1-week regimen of full-time EW was prescribed consisting of 6 nights of lens wear and 1 night without lens wear. If this EW schedule could be maintained without complications for 4 weeks, the subjects were considered "adapted" and proceeded to stage 3. Subgroups of CLEWS subjects were also asked to participate in a variety of laboratory assessments, including endothelial photomicroscopy and measurements of corneal hydration control, overnight corneal swelling, and epithelial permeability. Baseline laboratory data were taken on participating subjects during stage 2.

Stage 3. Randomized Lens Wear and Follow-up

Subjects entering stage 3 were randomly assigned to either a high- or medium-Dk lens group for 12 months of EW. Clinical assessment examinations were scheduled after randomization at 3, 6, 9, and 12 months. These examinations included an oral history, lens assessment, keratometry, manifest refraction, and a detailed slit-lamp examination. The slit-lamp examination included inspection of lids, conjunctiva, and cornea, with each of these areas further subdivided (e.g., bulbar and palpebral conjunctiva, central and peripheral cornea) for grading by clinicians of 17 possible ocular conditions (e.g., corneal staining, hyperemia, microcysts, infiltrates). Each subdivided area was graded on a 0 to 3 scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe) according to the Mandell Slit Lamp Classification Protocol.[15] Subjects participating in overnight corneal swelling measurements also had pachometry readings taken at 3-month intervals. Subjects who participated in baseline (i.e., prerandomization) endothelial photomicroscopy or corneal hydration control measurements had these procedures repeated at the final 12-month visit. Laboratory results from these subsets of CLEWS subjects will be reported in a separate article.

In addition to the regularly scheduled clinical visits of stage 3, subjects could report for unscheduled visits because of onset of adverse symptoms or at the request of the attending optometrist (e.g., to monitor development of subclinical keratopathy observed at a regular quarterly visit). During any phase of the study, subjects could elect to discontinue participation or be dropped from the study by decision of the clinician and principal investigator (PI). At the conclusion of the study, subjects were asked to discontinue lens wear for 1 week and report for a final clinical assessment.

Bias Control Measures

Randomization

We assigned subjects to the medium- or high-Dk lens groups by means of a stratified block-randomization scheme. Because age and gender were likely to be associated with outcomes, we used stratified randomization to balance these subject features across the study lens groups. That is, within strata defined by age ($\leq$30, $>$30 years) and gender, subjects were assigned to one of the two study lens groups using a randomized block scheme with assignments based on randomly permuted block sizes of two or four subjects. Block randomization ensured that, at most, four consecutive subjects within a stratum could be assigned to the same lens group. Permuting the block sizes (either two or four) ensured that study personnel who were also involved in recruitment activities remained masked as to future randomizations in that stratum. Overall, this randomization strategy ensured balanced allocation of subjects to the two lens groups throughout the course of the trial, thus protecting against possible biases in group comparisons resulting from temporal changes (e.g., altered eligibility criteria, personnel changes, instrument drift, procedural changes, observer criteria changes over time). To implement this scheme, we generated the randomized block assignments for each stratum using random number generating functions in SPlus (MathSoft, Inc., Seattle, WA).[16] These lists were then stored in SAS (SAS Institute, Inc., Cary, NC)[17] database tables and accessed by study personnel through an SAS application that included real-time verification of the subject's name, age, gender, and study identification number, ensured that the subject had complete stage 1 and 2 data entered on the study database, and verified that the subject had not already been assigned to a study lens group.

Masking

The PI, optometrists, and technicians were masked to the lens assignment of all patients at all times, as were the patients themselves, which was possible because the two study lenses were indistinguishable by visual inspection. The study coordinator required access to this information to place the lens orders but did not participate in subject examinations or data collection. The biostatistician also had access to this information but retained it in a separate data table that was rarely examined during the trial and was not aware of lens group assignments when making specific decisions about recruitment, retention, or data error resolution. Laboratory measurements were performed by technicians who were not aware of randomization assignments, and optometrists did not have access to laboratory data and referred to prior clinical examination records only when necessary for patient safety. Except in rare cases, each subject was seen by the same optometrist and technician for each examination throughout the study to control for interobserver variation.

Changes in Protocol from Original Design

Shortly after the start of the study, it became apparent that protocol changes were needed to improve subject recruitment and retention. After the first 6 months of active recruitment, it was evident that although an adequate number of subjects were attending orientation meetings, more subjects than expected were failing to reach stage 3 randomization. To attract a greater number of potential subjects and to improve subject retention in stages 1 and 2, we implemented four changes in the study protocol: (1) reduction of the proposed follow-up period from 3 years to 1 year; (2) relaxation of the requirement of no prior CL experience to permit some limited history of CL wear; (3) elimination of the arduous corneal hydration control measurements; and (4) reduction of the proposed no-CL wear period at the end of the 12-month follow-up from 3 months to 1 week. These changes were implemented less than 8 months after the start of recruitment, at which point only 13 subjects had been randomly assigned and only 3 of those had completed the first quarterly clinical assessment. These four changes allowed us to recruit and retain a sufficient number of subjects to complete the clinical trial with adequate statistical power to address our primary aims and without substantially altering the baseline demographic and ocular characteristics of our subject group.

Study Materials, Personnel, and Procedural Review

Lens Materials and Fitting Strategy. RGP lenses were selected for this study, because they are available in a range of oxygen transmissibilities in designs identical in every other respect. The medium- and high-Dk CLs used in this study (paflufocon B and paflufocon D) were made from a Siloxane-fluorocarbon polymer (Paragon Vision Sciences, Mesa, AZ), and both Dk materials have been used extensively for clinical RGP lens wear. The mean Dk of four randomly selected paflufocon B and paflufocon D lenses were 45×10^{-11} and 92×10^{-11} (cm^2/sec)(ml O_2/ml $\times$ mmHg), respectively, which are approved by the Food and Drug Administration for EW. On average, these lenses were made with a central thickness of 0.17 mm and varied from 0.12 to 0.22 mm in both Dk groups, which gives a range of oxygen transmissibility (Dk/t) of 21 to 38 and 43 to 77 (10^{-9} [cm $\times$ ml $\times$ O_2]/[sec $\times$ ml $\times$ mmHg]) for the paflufocon B and paflufocon D lenses, respectively. The average overall lens diameter for both lens materials was 9.2 mm. Lenses were fitted with a base curve radius that was slightly longer than the flat corneal meridian as measured by keratometry. For each 1.00 diopter of corneal toxicity (as measured by keratometry), the base curve radius was increased approximately 0.05 mm (i.e., 0.25 diopter). Secondary and peripheral curve radii were made to be 1.0 and 3.0 mm flatter that the central base curve, with widths of 0.2 and 0.3 mm for the secondary and peripheral curves, respectively. Criteria for an acceptable diagnostic fit included either lid attachment (i.e., lens riding slightly under the upper lid after the blink) or interpalpebral fit. In both cases we attempted to achieve optimal lens movement during the interblink period that would allow the lens to gravitate 1 to 2 mm toward the inferior lid margin with a slow vertical movement. An acceptable bearing relationship included an even distribution of fluorescein under the lens and an adequate peripheral lens tear reservoir (without excessive edge standoff).

Study Personnel. Both optometrists and optometric technicians participated in taking study measurements. The optometrists were CL specialists with considerable clinical experience in RGP design, fitting, and follow-up care, who were responsible for performing the initial eye examinations, CL fittings, epithelial permeability measurements, and all clinical examinations during the 12 months of EW. Optometric technicians were trained to perform pachometry, endothelial photomicroscopy and digitizing, lens verification, and subject training in CL handling procedures. All technicians successfully completed a rigorous certification process for each instrument and laboratory procedure and were periodically retested to ensure that they maintained a consistently high standard. In addition to the optometrists and technicians, the research team included a faculty biostatistician who, as co-PI for most of the CLEWS study, was instrumental in the design and implementation of the trial including review by a DSMB and the creation of data analysis strategies. A senior biostatistician was responsible for monitoring of recruitment and retention, database design and data management, and working with the faculty biostatistician and the PI in statistical analyses. A study coordinator was responsible for patient scheduling, implementing recruitment procedures (e.g., posting advertisements, contacting the clinic for information on referrals), organizing and filing all patient records, and some data entry and computer file management under the supervision of the biostatistician.

External Interim Review. CLEWS received institutional approval from the University of California at Berkeley Committee for Protection of Human Subjects. In addition, an independent DSMB was appointed to conduct an interim review of CLEWS with regard to safety and related issues. Members of the DSMB consisted of (1) an infectious disease physician/epidemiologist, (2) a biostatistician (chairperson), (3) a university-based optometrist with expertise in CL fitting, (4) an ophthalmologist with expertise in external disease, and (5) a community member. When approximately 60% of the study was complete, the DSMB received presentations concerning implementation of the study design, efforts to protect human subjects, and preliminary data related to safety. The DSMB concluded that the study was being conducted in a manner consistent with providing optimal protection to the subjects and that the study lenses had caused no adverse ocular events of a severity to warrant discontinuation of the study. The DSMB concluded that the alterations to the study design in response to recruiting and retention problems were timely and otherwise appropriate and that the study retained sufficient statistical power to achieve its primary aims. The committee recommended that the trial continue and that an additional meeting was not necessary unless new safety issues arose.

Data Management and Quality Assurance

The number and variety of measurements and observations performed under this study design generated a vast array of demographic, historical, clinical, and laboratory data. It was necessary to develop a method of data entry and verification that would permit their timely review for monitoring recruitment and retention rates and for assuring patient safety and high data quality. We used the Teleform system (Cardiff Software, San Marcos, CA),[18] which uses optical mark and character recognition for scanning data entry forms, provides tools for immediate verification of accuracy, and permits design of customized data entry forms that the optometrists could easily complete without disrupting the flow of the examination or rapport with the patient. The study coordinator was responsible for scanning forms, verifying data, and working with the clinicians and biostatisticians to resolve data entry errors. Details of the form design, data validation, and performance capabilities of the Teleform system have been reported elsewhere.[19]

After scanning and verification, the data were subjected to an extensive set of quality assurance (QA) programs written for the SAS system. The CLEWS QA system consisted of three levels of SAS programs: (1) within-form checks for missing data, valid data ranges and types, and logical relationships among form variables; (2) comparison of new batches of scanned data to the master CLEWS database, checks for duplicate forms, logical relationships between current and prior patient data, and errors in the sequence of visit dates; and (3) screening of the master database for logical inconsistencies between different variables across different visits. All laboratory data were also subjected to customized SAS QA programs.

The QA system generated reports that flagged discrepancies in the database that could represent either data entry errors or real changes in the condition of the patient requiring an investigation by the PI or attending optometrists (e.g., large changes in visual acuity). The QA reports were first screened by the biostatistician, and any data entry errors were resolved by referring to the data entry forms and, if necessary, consulting the study coordinator or optometrist. Flagged items that were not simple data entry errors could possibly indicate real changes in patient status and thus were referred to the PI for investigation. Data entry errors were more common by far than real changes, although we did occasionally encounter large changes in corneal curvature (e.g., $>$ 1.0 diopter) or reductions in visual acuity (e.g., $>$ 2 lines on the visual acuity chart) that prompted optometrist review of the patient records and scheduling of the patient for follow-up examinations. The QA reports did not reveal any previously unidentified adverse events severe enough to warrant discontinuation of a subject from the

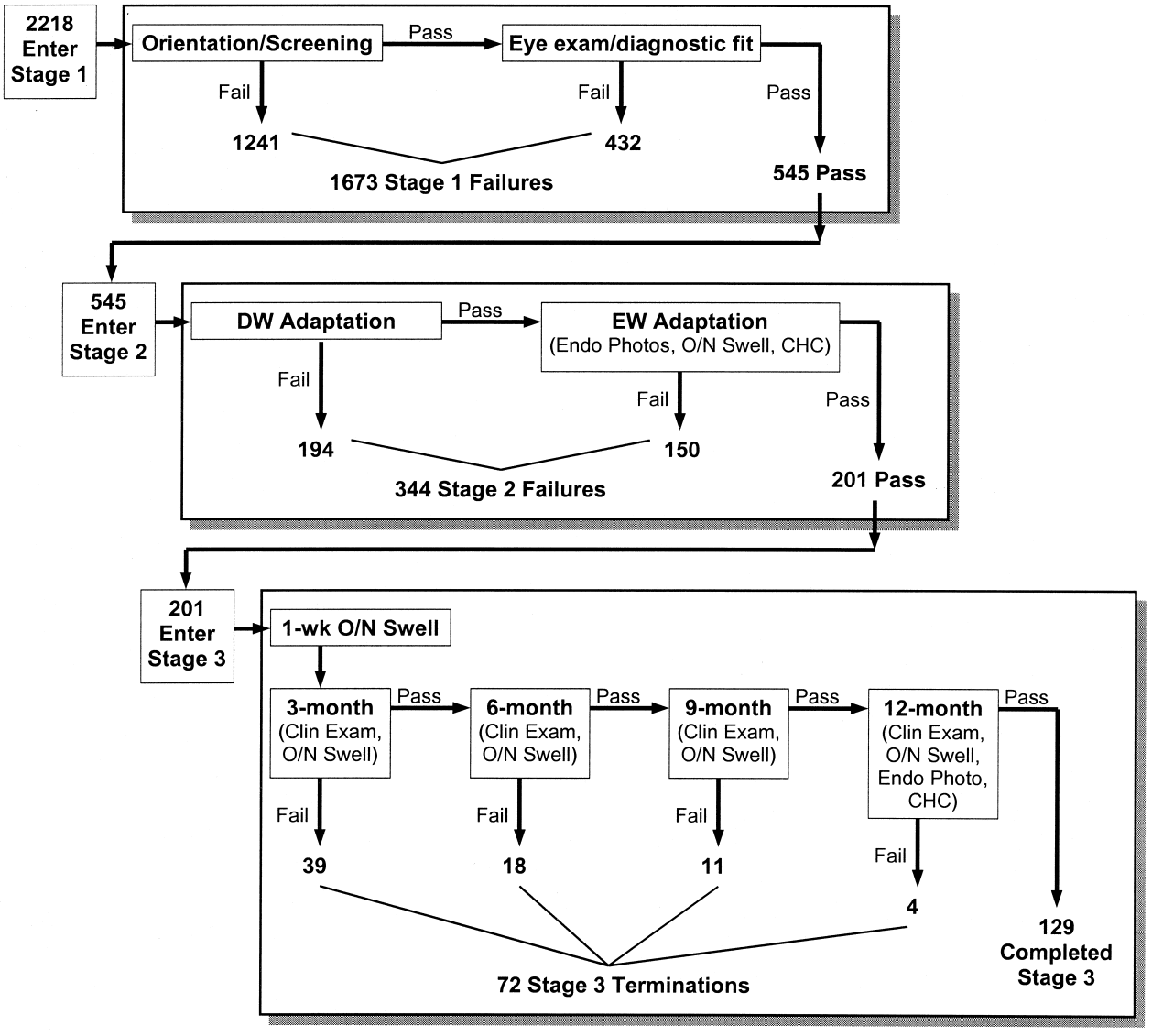

Figure 1. At any stage of the Contact Lens Extended Wear Study, clinical trial subjects could elect to discontinue participation, be dropped by the clinician, or successfully complete the stage and proceed to the next. Shown within each of the three stages are the number of subjects entering that stage, the various examinations and measurements performed, the number of subjects failing to complete these visits, and the number successfully completing all visits for that stage. The timeline at the bottom shows when data collection for each stage began and was completed over the course of the 5-year study. (CHC = corneal hydration control assessments; Clin Examination = quarterly clinical follow-up examinations; Endo photos = endothelial photomicrographs; O/N Swell = overnight corneal swelling measurements.) DW = day wear; EW = extended wear.

study. All CLEWS data, clinical records, laboratory readings, and QA reports were backed up at the instrument or scanning site, and multiple copies were stored outside the laboratory area. New data were backed up frequently as forms were scanned, QA reports completed, or instrument readings performed, whereas the master database was backed up monthly.

Results

Subject Recruitment and Retention

Figure 1 depicts the flow of subjects through the three stages of the trial from the beginning of recruitment to the end of data collection and termination from the study. A total of 2218 subjects responding to recruitment efforts entered stage 1 by attending a CLEWS orientation from April 1994 through December 1997. Of these 2218 prospective subjects, 977 met the initial eligibility criteria and were scheduled for comprehensive eye and CL fitting examinations. Of these 977 subjects, 545 subjects met all the requirements for CL wear and study eligibility and were dispensed high-Dk RGP adaptation lenses for entry into stage 2. Figure 2 shows the percentages of subjects who failed in either stage 1 or stage 2. Of the 2218 subjects who entered stage 1, a total of 1673 did not proceed to stage 2 (75%), the primary reasons being that they failed to meet eligibility criteria (59% of failures) or expressed a lack of interest in participating in CLEWS after the study requirements were fully explained (40%). Among the 545 who

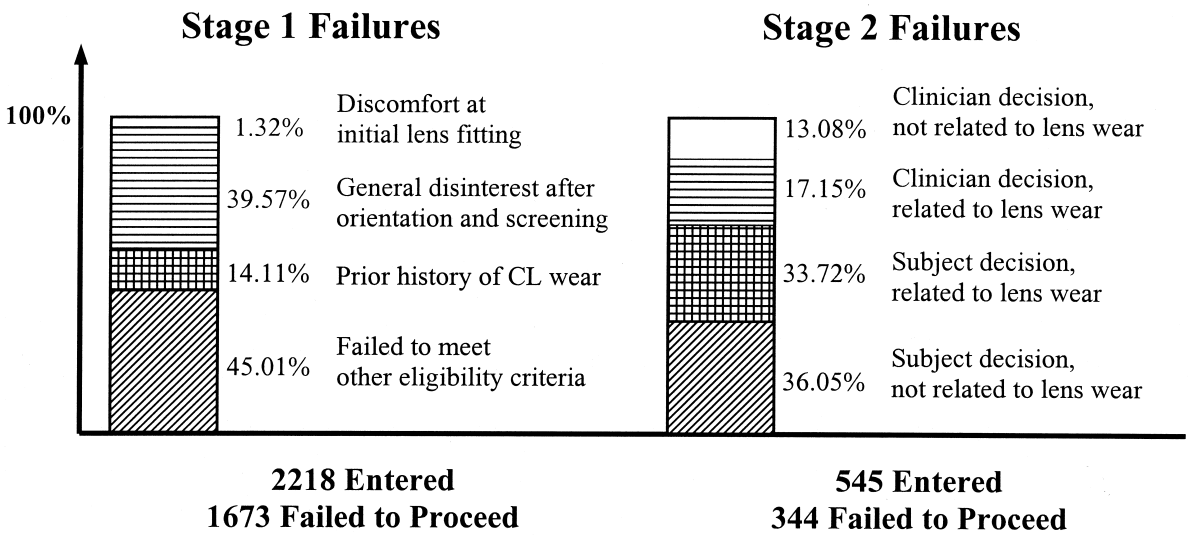

Figure 2. During stage 1 of the Contact Lens Extended Wear Study trial, subjects could discontinue participation either because of discomfort at the initial fitting or because of factors unrelated to contact lens (CL) wear (e.g., time commitment, moving residence out of the area), or study personnel determining that an interested potential subject did not meet eligibility criteria (approximately 14% for prior CL wear). Subjects entering stage 2 could elect to discontinue because of discomfort during adaptation to daily or overnight wear or for reasons unrelated to lens wear, whereas the clinician could drop a subject because of lens-related complications (approximately 17%) or noncompliance with the study protocol.

entered stage 2, 344 failed to reach stage 3 randomization (63%). Of those 344 subjects 17% had CL-related responses that were sufficiently important to discontinue lens wear (typically central corneal staining or persistent lens adherence), whereas another 34% of withdrawals were subject-initiated, primarily because of lens-associated discomfort. For the remaining subjects (49%) who did not proceed to stage 3, approximately 13% were dropped by the clinician because of noncompliance with the CL adaptation protocol, whereas 36% were due to issues not related to CL wear, such as moving out of the area, difficulty in maintaining a commitment to the study visit schedule, or nonocular related health issues.

Application of Hypoxic Dosage

The two study groups were allocated lenses with substantially different Dk. If all other lens parameters were kept constant, the two groups would have received two different levels of hypoxia corresponding to the different lens Dk. However, the amount of oxygen reaching the cornea is determined by the oxygen transmissibility (Dk/t), which is a function of both the permeability of the material and the thickness of the lens. Because lens thickness varies with vertex power and study lenses varied in power among CLEWS subjects, there was a range of Dk/t values for subjects within each Dk group. To verify that the medium- and high-Dk groups were subject to distinctly different hypoxic doses (i.e., different levels of oxygen reaching the cornea, determined by the Dk/t), we examined the distribution of Dk/t when lens thickness is taken into account for each subject. The histogram of Dk/t shown in Figure 3 reveals that, despite the variability within each Dk lens group caused by the subject-specific lens thicknesses, the distributions of oxygen transmissibility are completely disjoint between the two groups. We therefore conclude that the study groups did receive different hypoxic doses.

Internal and External Validity

Of the 201 subjects randomly assigned to study lenses, 103 subjects received the medium-Dk lenses and 98 received the high-Dk lenses. Table 2 lists the baseline (i.e., prefitting) characteristics of the two study groups and shows that the randomization scheme maintained balance between the two groups in age and gender. There were no important differences between the lens groups in mean age, gender or ethnic composition, proportion with prior CL history, mean corneal curvature, refractive error, or visual acuity. The close similarity of these groups in terms of their baseline characteristics ensures the internal validity of between-lens group comparisons (i.e., because the two groups are comparable with respect to the characteristics listed in Table 2, any apparent differences we observe between groups in study outcomes will not be due to confounding by these variables).

It is also important to compare the baseline characteristics of the 344 subjects failing stage 2 to those of the 201 subjects who entered stage 3 and whose data will be used in subsequent analyses, because differences between randomly assigned subjects and the original pool of eligible subjects might limit the external validity, or "generalizability," of our statistical results. That is, if the subjects who successfully adapted to RGP EW and entered stage 3 had different demographic or ocular features from the eligible candidates who were not able to adapt to EW, statistical results obtained using this sample would not necessarily be applicable to the general CLEWS study population as defined by the entrance criteria, adaptation criteria, and recruitment scheme. Table 3 shows the baseline characteristics of the 344 stage 2 failures and the 201 stage 3 randomly assigned subjects. As expected from the pool of potential subjects from the Berkeley campus and surrounding community, the mean age of initial entrants was roughly 23 years, approximately 85% of subjects were students (not shown in Table 3), and Asian-Americans and Caucasians accounted for approximately 75% of the ethnic makeup. Mean visual acuity, male-to-female ratios, and proportions of subjects with prior CL history were similar. Although there were very modest differences in mean corneal curvature and refractive error, such differences are insignificant clinically and within the usual measurement accuracy for these instruments. These comparisons show that the eligible candidates who were unable to complete EW adaptation did not display any clinically important differences

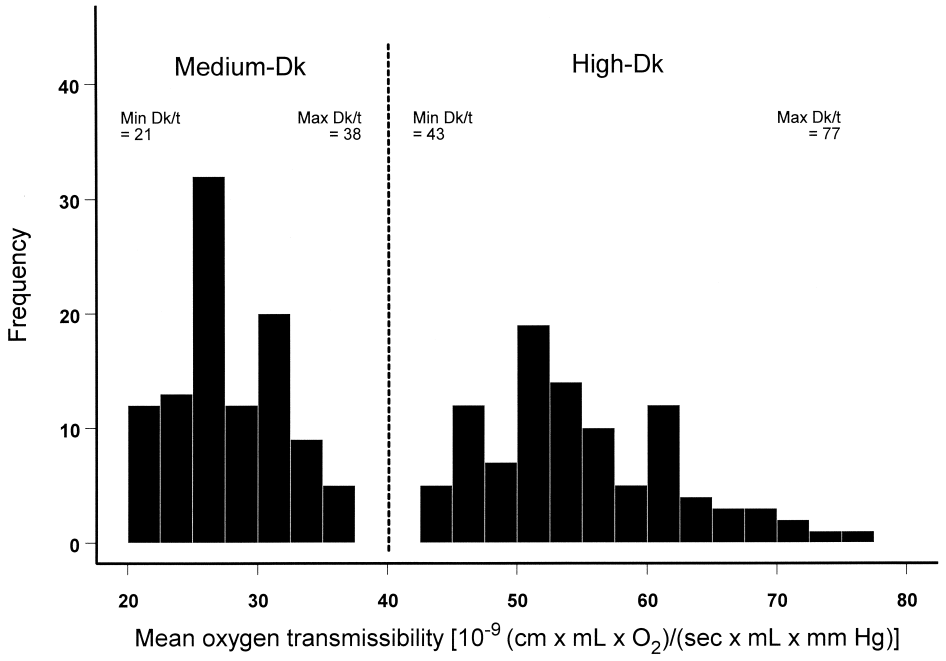

Figure 3. Although the two randomized study groups received lenses of different oxygen permeabilities (Dk), it was possible that the range of oxygen transmissibilities (Dk/t) caused by differences in lens thickness within each group could result in overlap in the hypoxic doses that the two groups received. The histogram shows that the distributions of Dk/t for the two groups were separated, confirming that distinctly different hypoxic doses were delivered to the study groups.

Table 2. Baseline Characteristics of Subjects who met Contact Lens Extended Wear Study Eligibility Criteria, Successfully Adapted to Rigid Gas-Permeable Extended Wear, and Were Randomly Assigned to Either the Medium- or High-Oxygen Transmissibility Group. The Similarity of These Characteristics in the Two Study Groups Ensures that Apparent Group Differences in Outcomes Will Not Be the Result of Confounding by These Variables

	Medium-Oxygen Permeability (n = 103)	High-Oxygen Permeability (n = 98)
Subjects with contact lens history (%)	22.33	18.37
Gender (%)		
Male	56.31	56.12
Female	43.69	43.88
Ethnicity (%)		
African American	5.83	6.12
Asian American	41.75	40.82
Caucasian	39.81	34.69
Hispanic American	4.85	10.20
Native American	0.97	1.02
Other	6.80	7.14
Mean age at orientation (years)	22.93	23.26
Mean corneal curvature (diopters)		
Horizontal meridian	43.41	43.55
Vertical meridian	44.12	44.18
Toricity	0.79	0.74
Residual astigmatism	1.27	1.23
Mean refractive error (diopter)		
Sphere	−2.91	−2.72
Cylinder	−0.48	−0.48
Equivalent sphere	−3.15	−2.96
Mean visual acuity		
log(1/Snellen fraction)	1.01	1.01

Table 3. Baseline Characteristics of Subjects Who Were Randomly Assigned vs. Those Who Began Stage 2 Lens Wear Adaptation but Failed to Proceed to Randomization. The Similarities between Eligible Subjects from Whom Data Were or Were Not Obtained Suggests that Statistical Inference from our Stage 3 Results to the General Contact Lens Extended Wear Study Population is Appropriate

	Failed Stage 2 Adaptation (n = 344)	Randomly Assigned to Stage 3 (n = 201)
Subjects with contact lens history (%)	23.26	20.40
Gender (%)		
Male	58.14	56.22
Female	41.86	43.78
Ethnicity (%)		
African American	7.56	5.97
Asian American	41.57	41.29
Caucasian	31.69	37.31
Hispanic American	10.47	7.46
Native American	0.29	1.00
Other	8.43	6.97
Mean age at orientation (years)	23.88	23.09
Mean corneal curvature (diopters)		
Horizontal meridian	43.20	43.48
Vertical meridian	43.82	44.15
Toricity	0.75	0.77
Residual astigmatism	1.15	1.25
Mean refractive error (diopters)		
Sphere	−2.52	−2.81
Cylinder	−0.41	−0.48
Equivalent sphere	−2.73	−3.06
Mean visual acuity		
log(1/Snellen fraction)	0.97	1.01

compared with the sample of 201 subjects who we randomly assigned and for whom we collected follow-up data.

Conclusions

In this article we have described the purpose, design, and conduct of the CLEWS clinical trial, the nature of the hypoxic treatment, the protocols used to control bias and ensure data integrity, and the baseline characteristics of the CLEWS study population.

In summary, CLEWS was appropriately designed to address the study hypotheses and was conducted with regard for the safety of the subjects and the integrity of study data. CLEWS adhered to rigorous protocols that were successful in controlling for bias and maintaining balance in the two study groups with respect to potential confounding variables. Finally, we have provided the information on our hypoxic treatment and the characteristics of our subjects necessary for evaluating and interpreting the results that follow in the companion article.

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